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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/523,948	10/17/2005	Dennis E. Hallahan	1242/57 PCT/US	9401

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EXAMINER	
GEMBEH, SHIRLEY V	
ART UNIT	**PAPER NUMBER**
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/523,948	HALLAHAN ET AL.	
	Examiner	Art Unit	
	SHIRLEY V. GEMBEH	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) *14 and 18-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13 and 15-17* is/are rejected.

7)☒ Claim(s) *1* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/21/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of claims 1-17 in the reply filed on 3/12/08 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Although Applicant did not traverse the Restriction/Election Requirement, Applicant states that that they reserve the right to file one or more divisional patent applications, and that the election of LY294002 are made without traverse to the extent that the examination will continue until all species have been examined or a non-allowable specie is found of instant claims 14-17.
Applicant elected the specie LY294002. The Examiner has expanded the specie to include previously non-elected specie. Not all of the non-elected specie is examined.

The Specie election is extended to include Genistein, Wortannin, SU6668 and SU1124. Claim 14 is withdrawn from consideration.

Status of Claims

Claims 1-46 are pending.

Claims 1-17 are elected, claims 1-13 and 15-16 are rejected in this office action. Claims 14 and 18-46 are withdrawn.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 4/21/05 is acknowledged and has been reviewed. However, items 1 and 2 are lined through as search results are not considered as a non patent literature.

Claim Objections

Claim 1 is objected to because of the following informalities: PI3K antagonist should be spelled out when first used as it is misread as either P13K or PI3K. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for LY294002, Wortmannin, SU6668, SU11248 and Genistein, does not reasonably provide enablement for the administration of a very wide variation of P13k antagonist to a target tissue in a subject. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2nd 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those

in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a prima facie case

Nature of the Invention: All of the rejected claims are drawn to a method for increasing the radiosentivity of a target tissue in a subject administering a PI3K antagonist, whereby the radiosensitivity of the target tissue is increased.

The nature of the invention is extremely broad in that it encompasses a very wide variation of the actual the actual treatment of a wide variation of tumors/cancer with the above compounds.

Breath of the Claims: The complex of nature of the claims greatly exacerbated by breath of the claims. The claims encompass using wide variation of compounds of PI3k antagonist for increasing radiosensitivity in a wide variation of tissues. .

Predictability of the Art: The lack of significant guidance from the specification or prior art with regard to what compound is effective for treating what cancer is missing. Due to the wide variation of compounds for the treatment of cancers in general makes practicing the claimed invention unpredictable, because the existence of such is contrary in the understanding of pharmacotherapeutics is difficult. For example, Eckhardt (Journal of Laboratory and Clinical Medicine, Volume 147, Issue 3, March 2006, Pages 108-113), teach Cytotoxic drugs were designed to kill tumor cells, whereas agents of molecular targeted therapy inhibit various molecular functions of the

tumor cell. Consequently, their toxicity profiles also differ. Molecular targeted agents, except for monoclonal antibodies, are enumerated here in three classes: compounds active extracellularly, extra/intracellularly, and intracellularly. Although no major breakthrough has occurred in the drug treatment of neoplastic diseases yet, such compounds as trastuzumab, cetuximab, bevacizumab, gefitinib, erlotinib, imatinib, and bortezomib have shown considerable clinical promise. Major obstacles to the further development of molecular targeted compounds are described. The use of different endpoints, positron emission tomography for evaluation and predictive genetic markers are recommended. Combination therapy with cytotoxic drugs and studies in an adjuvant setting are also recommended. It is concluded that cautious optimism about the future of molecular targeted therapy is reasonable. See abstract.

Further, treatment of cancer in general is at most unpredictable, as underscored by Gura (Science, v278, 1997, pp.1041-1042) who discusses the potential shortcomings of potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with clonogenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, 1St column) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive. Also Jain (Sci. Am., 1994, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col. 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic

agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col. 3).

In view of the teachings above, and the lack of guidance and or exemplification in the specification, it would not be predictable that the method would function as contemplated. Thus, it would require undue experimentation by one of skill in the art to practice the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 8, rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

What is meant by "administering a minimally therapeutic dose"? What is the lower limit for minimally therapeutic dose?

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-10 and 12-13 are rejected under 35 U.S.C. 102(e) as being anticipated by Durden US 6,777,439.

Durden teach regulating p53 mediated gene expression by administering P13kinase inhibitors to increase chemosensitivity/radiosensitivity of tumor cells (brain tumors), wherein the PI3k antagonist is LY294002. See col. 2, lines 29-31, 45-55 and 64-67, col. 3, lines 1-3 and col. 7, lines 9-40 as required by instant claims 1, 4, 8 and 12. As to instant claims 10 wherein the PI3K is Wortmannin, see col. 52, lines 39-40. Ly294002 was administered at 100 mg/kg wherein the subject is a mammal (mice) see col. 37, lines 28-30 as required by instant claims 7-8 and 13. With regards to instant claims 2-3 the reference teaches the target tissue to be a vascular endothelial tumor (brain), see col. 25 and 26, lines 63-67 and lines 127. As to instant claim 6 wherein the target tissue is a vasculature supplying blood flow is taught see col. 36, lines 44-47. The reference further teaches the P13K regulates the proliferation of new blood supply as required by instant claim 6 col. 36, lines 40-48. The PI3K is administered in a pharmaceutical carrier as required by instant claim 9, see col. 22, lines 2-9.

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-9 and 15are rejected under 35 U.S.C. 102(a) as being anticipated by National Cancer Institute (Clinical Trials) 9/1/2001 first published, 4 pages. The reference teaches administering SU6668 to patients (human-mammal) with solid tumors at an optimal biological effective dose anticipitates the therapeutic index was minimal since toxicity is of concern with every drug use. See underlining as required by instant

claims 1-9 and 15. It is anticipated that the administration will target tissues such as endothelial tissues and vascular tissues as required by instant claims 2-3. Tumors are resistant to radiation as evidence by Vaupel et al. See underlining abstract (evidence by Vaupel et al. Medical Oncology, 18(4), 2001 Abstract only) because advance solid tumors are characterized in that manner. It is anticipated that once the compound/drug is administered the function increasing radiosensitivity will be inherent function of the compound. As to the target tissue being endothelial and vascular, it is anticipated as these cells are thin layer of cells that line the interior surface of blood vessels of the entire circulatory system which the entire body is made up of. It is anticipated that the drug is in a pharmaceutical carrier, since the reference teach a clinical trial of the drug in humans as required by instant claims 7 and 9. Claim 15 for example identifies SU6668 as a PI3K antagonist therefore the limitation of PI3K is met. It is the Examiners' position that because the drug is administered to humans it is in a pharmaceutically acceptably carrier.

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7 and 15 rejected under 35 U.S.C. 102(b) as being anticipated by Laird et al. Cancer Res. 2000 Aug 1;60 (15):4152-60 10945623 (P,S,E,B) Cited:3 (Abstract Only).

The reference teaches vascular endothelial growth factor is associated with solid tissue and SU6668 is a novel inhibitor of solid tumors. Increased radiosensitivity of the target tissue is produced by the administered PI3K as recited in claim 1 is the effect of the PI3K therefore, administration of SU6668 by Laird in the clinical trial would

inherently produce the same effect because a compound/composition and its properties cannot be separated. The reference teaches that further clinical trials are on going in mamalian patients and since the clinical trials involve administration of the SU6668 PI3K as a pharmaceutical, it flows that the SU6668 PI3K is in a pharmaceutical composition.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-13 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Durden US 6,777,439 taken with Walker et al. Molecular Cell, Vol. 6, 909–919, October, 2000, in view of Weichselbaum et al. US 6,025365

Durden (see supra) is applied here. Further Durden teaches administering Wortmannin at concentration 10, 5 and 1 μg/ml but fails to teach the administration in mg/ml. The reference fails to teach the concentration per mg/kg of the Wortannin and fail to expressly teach the tumor is a radiation resistant tumor, a dominant polypeptide SU6668 and SU11248 and a pharmaceutical carrier.

Walker et al. teach LY294002, Wortmannin and Genistein are all PI3k inhibitors as required by instant claims 1, 8, 9 in part, 10, 12 and 17, it is expected that the functions of the agents would be the same that is will increase the radiosensitivity of a target cell when administered absent factual evidence. Also as stated in the MPEP 2112.01"Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

While Durden et al, do not teach expressly the tumors are radiation resistant it is known in the art that glioblastomas are resistant to radiation as taught by Weichselbaum et al. teach glioblastoma is a radiation resistant tumor, see title and col. 11 lines 35.

Thus taking the combine teachings of the references, one having ordinary skill in the art at the time the claim invention was made would have reasonable expectation of success that administration of SU 6668 in µg/ ml or mg/ml would increase the radiosensitivity of the tumor for treatment.

One of ordinary skill in the art would have been motivated to combine the cited prior art and administer a PI3K antagonist for increasing radiosensitivity in a targeted tissue because it has been taught in the prior art before to the instant invention. See col. 40, lines 54-60 US 6777439.

As to the administration of the Wortannin in the concentration claimed, one of ordinary skill in the art would have been motivated to optimize the concentration. Based on that the determination of a dosage having the optimum therapeutic index is well within the level of the ordinary skill in the art, and the artisan would be motivated to determine the optimum amounts to get the maximum effect of the drug, hence the reference makes obvious the instant invention.

Claims 1 and 15-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Durden US 6,777,439 in view of Ning et al. Radiation Research 157, 45-51 (2001) published January and Cancer Institute (Clinical Trials) 9/1/2001 first published, 4 pages further in view of Tang et al. 6,573,293.

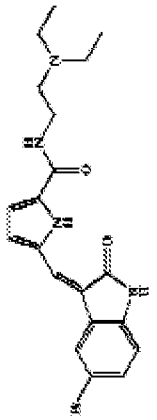
Durden teach regulating p53 mediated gene expression by administering PI3kinase inhibitors to increase chemosensitivity/radiosensitivity of tumor cells (brain tumors), wherein the P13k antagonist is LY294002. See col. 2, lines 29-31, 45-55 and 64-67, col. 3, lines 1-3 and col. 7, lines 9-40 as required by instant claim 1. The

reference did not teach the use of SU6668 or SU11248 or negative PI3K polypeptide as the PI3K antagonist.

Ning et al. teach SU6668 enhances the efficacy of radiation therapy in mice bearing carcinomas, see underlining. It is noted that the reference did not name the SU6668 as PI3K antagonist, however, the compound as used functions the same as claimed by the instant application. "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established.

Cancer Institute (Clinical Trials) is applied here as above.

Tang et al. Teach pyrrole substituted 2-indole compounds that modulate the activity of protein kinases disorders. See abstract. The reference further teach the

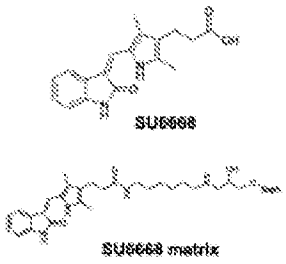


compound is SU11248

One of ordinary skill in the art would have been motivated to use any of the tyrosine kinase inhibitors to enhance the radiosensitivity of a targeted tissue because abnormal growth activities have been related to protein tyrosine kinase especially in disease such as brain cancer (glioblastoma). It is also taught that SU11248, inhibits

vascular endothelial growth factor receptor 2, platelet-derived growth factor receptor, c-kit, and fetal liver tyrosine kinase 1. See col. 166, lines 20-67. Based on the multitarget aspect of the tyrosine inhibitor one of ordinary skill in the art would have been motivated to administer any of the claimed drugs and expect success in doing so.

Furthermore the core structures of SU6668 and SU11248 are the same, one of ordinary skill in the art would have been motivated to use either and expect increase radiosensitivity to targeted cell when administered because A prima facie case of obviousness may be based solely upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. In re Deuel, 51 F3d. 1552, 1559 (Fed. Cir. 1995). The necessary motivation to make the claimed compound, and thus the prima facie case of obviousness, arises from the reasonable expectation that compounds similar in structure will have similar properties. In re Gyurik, 596 F.2d 1012, 1018 (1979). Structures of SU6668 is



No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHIRLEY V. GEMBEH whose telephone number is (571)272-8504. The examiner can normally be reached on 8:30 -5:00, Monday- Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

SVG
5/27/08